

Original Article

The value of PSA and its derivative indexes on improving the discrimination between NIH-IV prostatitis and prostatic cancer within the tPSA range 4-20 $\mu\text{g}/\text{mL}$

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Abstract: Objectives: To reduce unnecessary biopsy, tPSA, f/t, PSAD, TZPSAD and PZPSAD were analyzed to find if they perform differently in differential expression and diagnostic efficacy between NIH-IV prostatitis (AIP) and prostate cancer (PCa) among patients within the tPSA range of 4-20 $\mu\text{g}/\text{L}$. Methods: tPSA samples within a range of 4-20 $\mu\text{g}/\text{L}$ were collected and prostate biopsy punctures were performed in 1290 male patients with complete transrectal ultrasound data from December 2004 through September 2015 in our hospital. 152 patients (≥ 40 years old) with AIP or PCa were screened. We compared the two groups of data using a Wilcoxon signed-rank test. Analysis with ROC curve and Youden index (sensitivity + specificity - 1) was used to determine the best threshold for diagnosis. Results: There were 46 cases of AIP and 106 cases of PCa by pathologic diagnosis. There was significant difference in PSAD and TZPSAD values for AIP and PCa groups ($P < 0.01$), but no statistical difference was found when comparing PSAD and TZPSAD's area under the ROC curve ($P=0.366$). The best threshold for diagnosis is PSAD= $0.23 \mu\text{g}/\text{L}/\text{cm}^3$ or TZPSAD= $0.44 \mu\text{g}/\text{L}/\text{cm}^3$. The diagnosis thresholds for positive rate of PCa separately increase to 81.4% (79/97) and 83.0% (83/100) from the original value 70.0% (106/152). Therefore, 60.9% (28/66) and 63.3% (29/46) of AIP cases would avoid unnecessary prostate biopsy. Conclusions: PSAD and TZPSAD can differentiate middle aged to elderly patients with AIP and PCa. Potential prostate cancer patients who have PSAD $< 0.23 \mu\text{g}/\text{L}/\text{cm}^3$ or TZPSAD $< 0.44 \mu\text{g}/\text{L}/\text{cm}^3$ require additional attention if they have AIP.

Keywords: Prostate-specific antigen, prostatic neoplasms, prostatitis, PSAD, TZPSAD

Introduction

Prostate cancer is the highest incidence of male disease in the United States. Although China has a lower incidence, it increases every year [1]. The conventional PSA gray zone range is between 4 and 10 $\mu\text{g}/\text{L}$. Due to racial differences in the incidence of prostate cancer, some scholars believe the range from 4 to 20 $\mu\text{g}/\text{L}$ should be the Chinese PSA gray zone range reference [2, 3]. For prostate cancer suspicious patients with tPSA from 4 to 20 $\mu\text{g}/\text{L}$, only 21.0%-27.9% of prostate biopsies are diagnostic of prostate cancer [3-5]. According to many reports, many unnecessary prostate biopsies are performed if criteria for biopsy is solely tPSA value. Free PSA and derivative indexes including free-to-total PSA ratio (f/t), PSAD and TZPSAD can help to improve the specificity of prostate cancer diagnosis [4,

6-10]. However, most people focus on the PSA and derivative indexes between prostate cancer and prostatic hyperplasia; few scholars seriously believe that PSA derivative indexes improve the differentiation of prostate cancer from NIH-IV prostatitis. It is well known that PSA is not a specific indicator of prostate cancer diagnosis and that prostatitis can cause elevated PSA. Because NIH-IV category prostatitis (AIP) is clinically silent, potential patients with prostate cancer are easily overlooked before clinical diagnosis and treatment, causing unnecessary prostate biopsies for patients with AIP. After collecting data from patients who have undergone prostate biopsies in the past 11 years at our hospital, this paper discusses the diagnostic significance of tPSA, f/t, PSAD, TZPSAD and PZPSAD for discriminating middle aged to elderly patients with AIP and prostate cancer.

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Table 1. Prostate data from selected patients

		Total prostate volume/cm ³	Transition zone volume/cm ³	Peripheral zone volume/cm ³
AIP	Median	59.05	32.85	22.45
	Range	22.28~120.41	5.59~89.80	8.97~50.08
PCa	Median	38.75	14.80	20.85
	Range	14.50~122.99	1.63~107.02	8.04~100.28
P-value		<0.001	<0.001	0.346

Table 2. PSA and related values comparison between AIP and PCa groups

		tPSA (µg/L)	f/t	PSAD (µg/L/cm ³)	TZPSAD (µg/L/cm ³)	PZPSAD (µg/L/cm ³)
AIP	Median	11.23	0.15	0.22	0.35	0.58
	Range	4.88~20.00	0.03~0.48	0.08~0.52	0.11~2.80	0.16~1.44
PCa	Median	12.50	0.14	0.31	0.78	0.58
	Range	4.94~20.00	0.08~0.38	0.07~1.08	0.15~7.42	0.08~2.05
P-value		0.235	0.078	<0.001	<0.001	0.310

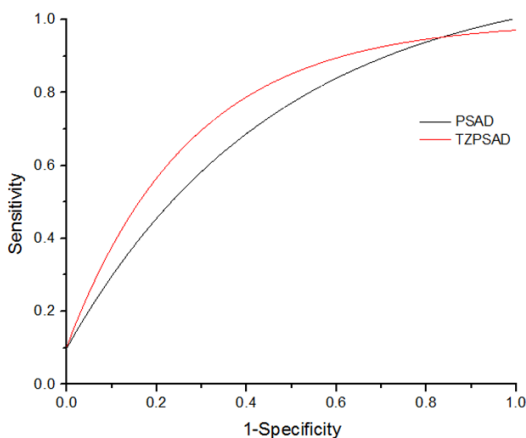


Figure 1. ROC curve for PSAD and TZPSAD in PCa case. $AUC_{PSAD}=0.704$ ($P=0.000$), $AUC_{TZPSAD}=0.759$ ($P=0.000$), no statistical difference between AUC_{PSAD} and AUC_{TZPSAD} ($P=0.366$).

Materials and methods

This study collected 1290 male patients' data in our hospital from December 2004 to September 2015. All patients with 4-20 µg/L tPSA received transrectal ultrasound guided prostate biopsy. Among these patients, 152 screened patients at age 40 or above had a diagnosis of AIP or PCa; these 152 were chosen as the research subjects. Their age range is from 42 to 84 years with median age of 69 years. Patients with prostatitis in this study were found by biopsy. They had no symptoms, such as discomfort or pain in the perineum, fre-

quency, or incomplete bladder emptying. All the selected subjects had normal reptilase times, urine and stool test results when first admitted. Before biopsy, patients had no history with acute or chronic urinary retention, catheterization, transurethral instrument operation (cystoscopy, transurethral prostatectomy, etc.), or ejaculation with digital rectal examination. Patients had no 5-alpha reductase inhibitors or any other history of medications

that affect androgen levels. This study was approved by the ethics committee of First Affiliated Hospital of Sun Yat-sen University.

Method

PSA, B ultrasound and biopsy: All patients had peripheral blood collected before having transrectal ultrasound and prostate biopsy. Blood samples were tested for serum tPSA, fPSA and f/t in our hospital laboratory. Our experienced urologist conducted transrectal ultrasound and prostate biopsy by using US GE LOGIQ 400 PRO ultrasound. First we measured transverse, anteroposterior and longitudinal diameter for prostate and transition zone using a 5.5-7.5 MHz probe. Then we obtained tissue samples by 18G biopsy needles for pathological examination using ultrasound probe E721. The biopsy needles number ranged from 6 to 12.

Calculation formulas:

Prostate volume=transverse diameter × anteroposterior diameter × longitudinal diameter × 0.52

Transition zone volume was calculated by using the same formula as prostate volume.

Peripheral zone volume is represented by the difference from prostate volume and transition zone.

$f/t=fPSA/tPSA$

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Table 3. PSAD and TZPSAD comparison under the ROC curve (AUC)

	AUC	S.E	95% CI	Z	P
PSAD	0.704	0.045	0.615~0.793	0.903	0.366
TZPSAD	0.759	0.041	0.678~0.840		

Table 4. Prostate biopsy data when PSAD=0.23 µg/L/cm³ (Unit: people)

		Pathological diagnosis		Total
		PCa	AIP	
PSAD	≥ 0.23 µg/L/cm ³	79	18	97
	< 0.23 µg/L/cm ³	27	28	55
Total		106	46	152

Table 5. Prostate biopsy data when TZ-PSAD=0.44 µg/L/cm³ (Unit: people)

		Pathological diagnosis		Total
		PCa	AIP	
TZPSAD	≥ 0.44 µg/L/cm ³	83	17	100
	< 0.44 µg/L/cm ³	23	29	52
Total		106	46	152

PSAD=tPSA/total prostate volume

TZPSAD=tPSA/transition zone volume

PZPSAD=tPSA/peripheral zone volume

Statistics (using SPSS19.0, EXCEL2003 and ORIGIN9.0)

According to biopsy results, patients were divided into AIP group and PCa group. Because the data was not normally distributed, statistics are described using Median and Range. Using the Mann-Whitney test, all statistical tests were 2-sided with a P < 0.05 considered to be statistically significant.

Using ROC curve to determine diagnostic performance: after calculating the Youden index (sensitivity + specificity - 1), the greatest Youden index indicates the best threshold for diagnosis.

Results

Biopsy results showed 46 cases of AIP and 106 cases of PCa. The median age for AIP and PCa

group are 67 years (42-84 years) and 70 years (49-82 years), respectively. The age between the two groups is not statistically significant (P=0.088). Patients' total prostate and transition zone volumes in AIP transition zone volumes are significantly larger than PCa group (both P < 0.01). However, peripheral zone volumes in two groups have no obvious differences (P=0.346). Details are listed in **Table 1**.

Comparison and analysis of PSA and related values between AIP and PCa groups: tPSA, f/t and PZPSAD are not statistically significant between the two groups when tPSA is within 4-20 µg/L. However, PSAD and TZPSAD are statistically significant (P < 0.01) (**Table 2**). PSAD and TZPSAD areas under the ROC curve are 0.704 and 0.759, respectively, both statistically significant (P < 0.01, **Figure 1**). However, there is no statistical significance when comparing their AUC (P=0.366, **Table 3**). Therefore, PSAD and TZPSAD have similar ability to identify AIP and PCa.

Diagnostic performance by using ROC curve and Youden index: (1) The most effective diagnosis threshold with the highest Youden index is when PSAD is 0.23 µg/L/cm³. The sensitivity and specificity of PCa were 73.6% and 67.4%, respectively. Positive and negative predictive values were 83.9% and 52.6% (**Figure 1**). If 0.23 µg/L/cm³ PSAD is used as the threshold for biopsy, it will avoid 60.9% (28/46) of unnecessary biopsies for patients with AIP. The prostate cancer diagnosis rate can be improved to 81.4% (79/97) from 70.0% (106/152) (**Table 4**). (2) The most effective diagnosis threshold is when TZPSAD is 0.44 µg/L/cm³. The sensitivity and specificity of PCa were 78.3% and 65.2%, respectively. Positive and negative predictive values were 83.8% and 56.6% (**Figure 1**). If 0.44 µg/L/cm³ TZPSAD is used as the threshold for biopsy, 63.0% (29/46) of unnecessary biopsies will be avoided for patients with AIP. The prostate cancer diagnosis rate can be improved to 83.0% (83/100) from 70.0% (**Table 5**).

Discussion

Under normal circumstances, the physiological barrier composed of basement membrane, basal cells and endothelial cells between the prostate acini and the lymphatic system limits

the amount of PSA from the glandular epithelium from entering into the circulation. When this barrier is damaged by tumors, a great amount of PSA goes into the blood circulation. Therefore, PSA is specific for processes occurring with prostate tissue but not specific for only prostate cancer. In 1995 the National Institute of Health (NIH) classified prostatitis into 4 categories: I: acute bacterial prostatitis; II: chronic bacterial prostatitis; III: chronic prostatitis/chronic pelvic pain syndrome; IV: asymptomatic inflammatory prostatitis. NIH category IV prostatitis is difficult to diagnose. Diagnosis of NIH-IV prostatitis is usually based on findings in prostatic fluid, seminal plasma and tissue samples from prostate biopsy. Thus, increased PSA from prostatitis is usually mistakenly attributed to prostate cancer. A survey conducted by Chinese specialists with 1868 normal male patients reported that the prevalence rate for NIH-IV prostatitis is 21.1% [11]. Foreign specialists report that prevalence rate for NIH-IV prostatitis is 32.2% [12] and the tPSA level in patients is higher than normal individuals. Engelhardt and others [13] analyzed pathological tissue after surgery and found there are 43.86% and 70.74% for patients with PCa and BPH combined with AIP, respectively. These studies show that AIP is not a rare disease and has an influence on PSA levels [14-16] that increases the number of unnecessary prostate biopsies.

There are increased tPSA levels in patients with prostate cancer, whereas fPSA levels are decreased. Patients with AIP have similar changes in tPSA and fPSA. This probably relates to the increased alpha1-ACT and alpha2-macroglobulin secreted by the liver during the inflammatory response. As a result, combined PSA is increased, whereas fPSA and f/t are reduced [17]. Austrian researchers point out that there is no difference in tPSA between AIP and PCa when tPSA > 4 µg/L, but that the f/t index has significant value for diagnosis. But when the data are analyzed to exclude excessive PSA levels and tPSA ranges from 4-10 µg/L, f/t has no ability to identify AIP and PCa [14]. Jung and others also confirmed that tPSA cannot differentiate PCa from AIP when the value is within the 4-20 µg/L range [18]. This outcome is similar with our data, which shows that when PSA falls within the "grey area" (4-20 µg/L range), tPSA and f/t levels for AIP and

prostate cancer are similar. It is difficult to differentiate PCa and AIP based on tPSA and f/t values.

Aside from tPSA and f/t, PSAD, TZPSAD and PZPSAD also have potential to aid with differentiation of prostatic diseases. Generally a PSAD level of 0.15 µg/L/cm³ is the decision threshold for prostate biopsy [19]. However, the majority benign prostate diseases are prostatic hyperplasia; PSAD of 0.15 µg/L/cm³ is not an effective threshold to differentiate between NIH-IV prostate and prostate cancer for middle aged and elderly patients. Although TZPSAD is less commonly used clinically, it can significantly enhance the ability to diagnose prostate cancer [2], beyond even PSAD [10]. There are no literature reports that use TZPSAD as a diagnostic tool for NIH-IV prostate and prostate cancer. PZPSAD is a newly derived parameter for PCa [20] and its diagnostic abilities for PCa require further investigation.

For patients with suspected prostate cancer, some researchers believe prostate volume for chronic prostatitis is larger than for PCa [21]. Our study shows the prostate volume for NIH-IV prostate is significant larger than PCa's and that the difference is greatest in the transition zone. The tPSA levels for AIP and PCa are similar, so PSAD and TZPSAD in patients with AIP are significantly lower than patients with PCa (P < 0.001). PZPSAD levels have no significant difference between AIP and PCa. This can be explained since prostate cancer has a high chance to developing in the peripheral zone; the transition zone volume has no significant change. On the other hand, chronic prostatitis has a high chance to occur in both the peripheral and transition zones [22]. PSA levels in patients with prostatitis and inflammatory infiltration range are positively correlated [15]. Inflammatory edema easily affects the entire prostate, increasing the size of both the peripheral zone and transition zone. It turns out that patients with NIH-IV prostatitis and increased PSA have lower transition zone PSA density than patients with prostate cancer. And there is no difference in PSA density in the peripheral zone.

Currently, the relationship between prostatitis and prostate cancer is still a controversial topic. For example, in the United State, Krieger

and others [23] conducted an epidemiologic study to show that prostatitis is a risk factor for prostate cancer. In Canada, Karakiewicz et al. [21] analyzed 4526 prostate tissue samples to show that prostatitis is a protective factor for prostate cancer. The causes of chronic prostatitis are unclear. It may relate to infection by a pathogenic microorganism. Ugurlu et al. made a comparison between patients with prostatitis and increased PSA taking levofloxacin or naproxen sodium. The results show decreased PSA levels in the group taking levofloxacin [24]. Bozeman et al. reported that 46.3% patients with chronic prostatitis have a normal PSA level after antibiotic treatment [25]. Ping Tang et al. [16] show that 41.2% of AIP patients with increased PSA have PSA drop below 4 $\mu\text{g/L}$ after antibiotic treatment. This means using 4 $\mu\text{g/L}$ tPSA as a biopsy threshold can result in unnecessary biopsy for 41.2% of patients. Therefore, for patients with low but increasing tPSA, especially for those patients with potential prostate cancer who have PSAD < 0.23 $\mu\text{g/L/cm}^3$ or TZPSAD < 0.44 $\mu\text{g/L/cm}^3$, we believe an initial trial of antibiotic treatment followed by reevaluation of PSA and other indexes to decide if biopsy is required. However, this hypothesis needs further prospective studies to validate. When considering asymptomatic inflammatory prostatitis, patients' ages, smoking history and education background [11] are important factors. In addition, patients' clinical symptoms, the digital rectal exam, ultrasound results, and performing necessary prostate fluid and seminal plasma exams can avoid unnecessary biopsy without overlooking prostate cancer.

This is a retrospective study so it has its own limitations. Most of the objects in this study had 12-puncture biopsies, but the few patients who received 6-puncture biopsies may have had a lower positive rate. Even experienced urologists that perform the biopsies and ultrasound exams have bias. These reasons can cause deviations in PSAD and TZPSAD values. In addition, pathologists usually do not comment on hyperplasia for patients with cancerous prostate, but these middle aged and elderly patients most certainly have some degree of prostatic hyperplasia. Because patients have no lower urinary tract obstruction symptoms and there is no obvious age gap between two groups, the influence from prostatic hyperpla-

sia in the two groups are similar. According to current knowledge, this study is the first to discuss the value of PSA and its derivative indexes on the relationship between asymptomatic inflammatory prostatitis and prostate cancer. However, the data comes from the largest hospital in southern China. Further investigations need to validate the results for other geographic and ethnic populations.

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Disclosure of conflict of interest

None.

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